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10/809,675	03/25/2004	Choong-Chin Liew	4231/2055C	8433

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
10/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/809,675	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,52,53,56-58 and 62-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50, 52, 53, 56, 57, 58, 62-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/16/08 has been entered.

2. This action is written in response to applicant's correspondence received 6/16/08. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive to place the claims in condition for allowance for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

3. Claims 50, 52, 53, 56, 57, 58, 62, 63, 64, and 65 are pending and examined in this office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 50, 52, 53, 56, 57, 58, 62, 63, 64, and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

The invention of claim 58 is drawn to a method a method for classifying NTN4 gene expression in a human "test subject", and sets forth steps of quantifying a level of RNA encoded by a NTN4 gene, comparing that level to a level of RNA found in blood samples from control subjects having osteoarthritis (OA) and also comparing it to control subjects who are healthy. The independent claim states that based on particular determinations, the classification of NTN4 gene expression results either with that of said subjects having OA or with that of subjects who are healthy. The nature of the invention requires the knowledge of a reliable association between NTN4 expression and the ability to classify a particular individual's expression with the expression of subjects having OA or not having OA, and further, the use of this method requires that there is an underlying assumption that this classification is meaningful. Reading the claims in light of the specification it is clear that applicant intends to use such a classification method in order to provide a tool that is used as part of a diagnostic process, and such a use requires the knowledge of a reliable association underlying the classification. Further, the practice of the invention requires an understanding of how the presence of osteoarthritis effects the level of NTN4 expression in human blood.

Newly added claim 62 recites a method of screening a human test subject for being a "candidate" for having osteoarthritis. The use of the word "candidate" in this context suggests that the method can be used to predict if someone might develop osteoarthritis. The active process steps in this claim are identical to those in claim 58, the claims differ only in the

preamble and the lengthy "wherein" clauses steps are very similar to those. The wherein clause sets forth that the test subject is a candidate for having osteoarthritis if the test level is statistically similar to that from subjects having osteoarthritis and statistically different from the levels in samples from said healthy subjects. The nature of the invention requires that a relationship is known whereby the expression of an individual's level of NTN4 predicts whether or not they will develop osteoarthritis.

All of the methods require comparing the test level with "quantified levels of RNA" from the control subjects.

Scope of the claims

The scope of the independent claim includes in step (b) patients who have OA as well as other possible conditions, including allergies, hypertension and control subject to systemic steroids. In fact, the claims are inclusive of patients who have OA plus any number of other co-morbidities such as rheumatoid arthritis or heart failure.

The claims recite that the finding of a "statistical difference" must be at a level where $p<0.05$ for some comparisons, but the claims are silent as to the finding of level statistical similarity for other comparisons. Even with the requirement of statistical significance, the this aspect of the claims remains quite broad since no particular level is required, and the claims even encompass using different levels of statistical significance for different comparisons. The phrase "statistically significant" describes a mathematical measure of difference between groups, not a particular level of difference which is acceptable. There is no universally accepted level of "statistically significant." The claims remain very broad in scope because they encompass that ANY level and direction of difference in gene expression between the tested subject and the

healthy controls or controls with OA is sufficient to result in a classification with the other group if the difference is "statistically significant" (provided there is also the required similarity) or sufficient to result in the individual being a "candidate" for having osteoarthritis. That is, the claims do not set forth that one level should be higher or lower than the other, and further do not set forth how much of a "difference" between two individuals would be necessary to draw the conclusions set forth in the claims.

Teachings in the Specification/Examples

Regarding osteoarthritis, the specification provides example 24 wherein gene expression profiles of blood samples from individuals having osteoarthritis were compared with normal individuals, that is healthy patients. The specification teaches that 300 genes were identified as being differentially expressed, and regarding the instant claims, table 3O provides a list of these genes (Example 24). NTN4 is among the genes.

The tables list genes that were differentially expressed, but does not provide any further information. For example, the tables do not teach if the expression was higher or lower in osteoarthritis patients versus controls.

The specification does not provide any guidance as to the level of "difference" that is sufficient (1 fold, 2 fold, etc) to result in a conclusion mRNA expression is properly classified as being in the "other" group, nor does the specification provide any guidance as to the direction of the difference (higher or lower expression) that is expected to be observed for any comparison of test subject versus the control groups. Notably, the specification also teaches that NTN4 is differentially expressed in the blood of patients who have rheumatoid arthritis versus healthy control patients (Example 22, Table 3M). In this case as well, the specification is silent as to the

nature of the difference in gene expression between patients with rheumatoid arthritis and healthy controls.

Additionally, NTN4 is not reported as being differentially expressed when tests are done with patients having osteoarthritis and hypertension as compared with normal patients (Table 3A), or osteoarthritis and obesity as compared with normal patients (Table 3B) or osteoarthritis and allergies as compared with normal patients (Table 3C), or osteoarthritis and subject to systemic steroids compared with normal patients (Table 3D). Furthermore, the gene does not appear in Table 3AB which provides genes that are differentially expressed in blood from patients with mild or severe OA but genes relevant to asthma, obesity, hypertension, systemic steroids and allergies have been removed. Thus, the gene is not differentially expressed in all patients with osteoarthritis.

Regarding claims 62-65, the specification only teaches that this gene is differentially expressed in the group of patients that have osteoarthritis versus those that are healthy controls. The specification provides no evidence to support a claim which encompasses identifying "candidates" insofar as this encompasses predicting that disease might develop.

The specification fails to provide information about an essential aspect of the invention, namely, the nature of the difference in expression that was observed between osteoarthritis patients and healthy patients. This information is essential to understanding and practicing the claimed invention. Each of the claims requires a comparison step with "quantified levels of RNA encoded by said gene in blood samples from control subjects" yet the specification provides absolutely no guidance as to what these levels might be or how the levels of control subjects who have osteoarthritis might differ from those who are healthy controls. These levels

also are not given in the prior art, particularly with regard to the control individuals who have osteoarthritis.

State of the Prior Art and Level of Unpredictability

The expression of genes in example 24 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication in the instant specification.

Observing differences in expression between two populations is a highly unpredictable endeavor. The specification clearly exemplifies this for the case of NTN4. The specification teaches differential expression of this gene between populations of patients with osteoarthritis and healthy controls. The specification also teaches that NTN4 is differentially expressed in the blood of patients who have rheumatoid arthritis versus healthy control patients (Example 22, Table 3M). So first, even if one carried out the claimed analysis on a test subject, and if one observed a level of expression, it is highly unpredictable how would one begin to know if that level of expression would properly be classified with patients having or indicative of candidacy

for osteoarthritis, rheumatoid arthritis, both, one but not the other, something in between or even some other condition or disorder for which the expression profile has not yet been determined.

Further, NTN4 it is not listed in the tables for differentially expressed genes in patients who have both osteoarthritis and other diseases or conditions versus normal controls. So, this exemplifies that a particular gene is not always differentially expressed in populations of patients having osteoarthritis versus healthy controls, and it also suggests that NTN4 expression could often be classified, according to the claimed methods, as being "with that of said subjects who are healthy" when the subject actually has OA. Observing the differential expression result is population dependent- something about patients with osteoarthritis and other diseases or conditions changes the observation. It is unknown and unpredictable whether this is also true for differential expression observations in other diseases. Furthermore, although NTN4 was not observed to be differentially expressed in any of the other examples in this specification, it is unknown and unpredictable whether it would be expressed in the blood of patients having other bone related diseases or other types of arthritis or any other diseases which were not tested in the instant specification or diseases which were tested in the instant specification but in a different population of test subjects, and whether this expression would be different from levels of expression in healthy controls. A method which relies on a comparison between expression in the blood of a test subject and control subjects requires the knowledge of this information in order to understand why it is relevant that expression of a gene in an individual is classified with subjects having OA or healthy subjects, as set forth in the claims. The instant specification has not established that all difference, no matter the magnitude nor the direction, relative to any control subjects or even relative to a healthy control subject is related to osteoarthritis (which is,

of course, what is suggested by classifying gene expression in said test subject with said subjects having OA). In fact, the specification shows that RA patients have a difference in this gene relative to healthy controls. It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have not been validated. But even if one were to obtain the same result, it would be unknown because applicant did not disclose the magnitude of difference in expression between osteoarthritis patients or controls, nor did applicant disclose the direction of variation. All of these inquiries are particularly important in this case since the specification is silent as to which differential expression observations would be sufficient understand how to use (i.e. apply) a method which classifies gene expression of NTN4 with OA patients or with healthy subjects.

Because the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a osteoarthritis or the absence of osteoarthritis cancer.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as

microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention. In particular, the specification does not provide adequate guidance to appraise one of ordinary skill in the art as to what levels of NTN4 gene expression must be observed for the conclusions set forth in the claims to be meaningful. Further, although the specification teaches there are differences in NTN4 levels in a osteoarthritis population versus a control patient population, the specification is silent as to the nature of the "difference" in magnitude or direction. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would begin by trying to reproduce the results observed in the instant specification to determine if there is a relative upregulation or downregulation of NTN4 in osteoarthritis patients versus healthy control patients, as the specification does not even provide this minimal guidance. Without this knowledge one would not even begin to know how to interpret any results obtained in practicing the claimed methods. For example, consider the comparison of a test result and a control population of healthy individuals. How different from the average level of expression of healthy individuals would the test result have to be to indicate osteoarthritis? Would any difference, up or down regulation be indicative of osteoarthritis? Or could one indicate osteoarthritis and one rheumatoid arthritis? Is NTN4 expressed in the blood of individuals with a disease other than rheumatoid arthritis and osteoarthritis? Is this expression also diagnostic of other degenerative diseases or other diseases of the joints or other disorders entirely unrelated to osteoarthritis? What populations could be tested and expected to provide a reliable result, as it is clear from the results in the specification that not all control subjects having osteoarthritis differentially express NTN4 relative to healthy controls? For example, if a subject has allergies, would the practice of the claimed assay be reliably informative in the event that NTN4 expression is different or the same as the control subjects? In order to reliably use a method for detecting osteoarthritis, one would first have to answer at least these questions. One would also, however, have to carry out this testing for validation, for it is possible that the result observed in the instant specification is intrinsic to the cohort of patients evaluated in applicant's study. Further, one would have to

undertake experimentation to determine difference thresholds required to determine that a patient has or does not have a disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of NTN4 in a test subject and comparing this expression to control subjects, wherein the results are used to "classify the expression" as being with OA subjects or with healthy subjects. The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Response to Remarks

Applicant traverses the rejection for lack of enablement, beginning on page 7 of the response.

Applicant reiterates that the specification has discovered an association between NTN4 expression and osteoarthritis, and that the disclosure supports the instantly claimed method of classifying NTN4 expression in a human test subject. The reasons that the examiner disagrees with this assertion are set forth in the rejection. Applicant disclosed that a difference in expression was identified but failed to disclose the nature of the difference. All of the claims require comparing the level of expression with quantified levels from control subjects, but the specification provides no guidance at all as to what these levels are. This is a critical feature of

the claimed invention, and a significant lack of disclosure. Complete reasoning for maintaining the rejection is given in the rejection.

Applicant disagrees with the examiner's assertion that an understanding of how the presence of OA effects the level of NTN4 expression in human blood is necessary to understand the invention. Applicant points out that there is no requirement of disclosing mechanisms. Here the intent of the statement was not to require that applicant disclose the mechanism by which the level of NTN4 expression is effected, but instead the nature of the effect. Applicant has not provided full disclosure of the relationship that was discovered.

Applicant points out that the instant claims are not drawn to methods of diagnosing osteoarthritis, nor to discriminating between patients that have OA and rheumatoid arthritis. This is noted, but not sufficient to overcome the rejection since even methods of classifying NTN4 expression as set forth would require undue experimentation to reliably practice given the limited disclosure in the specification, as discussed fully in the rejection.

Applicant disagrees with the statement in the rejection that observing differences in the expression of NTN4 between two populations is highly unpredictable, pointing out again that the claimed methods contain no resolution step of diagnosis of OA. However, the claims do include steps which "classify" expression or identify a test subject as a "candidate" for OA based on the recited comparisons, and in order for these to have any meaning, the underlying relationship must be predictable. In order for one of skill in the art to determine if this is the case, an inventive amount of experimentation must take place, as discussed in the rejection. Even if the claimed invention is being used as a preliminary tool in a diagnostic process, practicing the

invention in realistic setting would require one to know what outcome to expect in order to have some idea if the obtained result is reliable.

Applicant points out that in the Metabolite patent the assay for elevated homocystein levels could signal a risk of heart disease, while the claims of the Metabolite patent set forth that the elevated homocysteine in the body fluid is correlated with a deficiency of cobalamin or folate. Applicant points out that this issue was never raised in litigation regarding the validity of this patent. This is not a persuasive argument. First, the absence of the argument does not mean that it could not have been a valid point. But either way, in this case, it would be highly unlikely that an indication or classification of RA and OA be relevant to the same individual, while vitamin deficiency and heart problems might be concurrent. Here, there is no guidance as to how to discern between the possible presence of two disorders that would likely be exclusive of one another.

Applicant states that the classification of gene expression within a population is well established. The method cited by applicant, as stated in the specification generally requires a training phase and a testing phase before the classification tool is even developed. Here, the training phase has occurred, but the disclosure of the results is incomplete. Thus, in order to begin to reasonably use such a classification method, one or skill in the art would have to repeat (and validate) the training phase and then complete the testing phase. The outcomes of these phases are not predictable, and there is no guidance in the specification as to what the outcomes will be.

Applicant reiterates on pages 11 and 12 that they believe that it would not require undue experimentation to practice the methods of classification nor to determine the direction of change

in differential expression. Regarding the latter, applicant is reminded that the specification is required to teach what is essential for the practice of the claimed invention. Here the claims require comparing test values to control values where absolutely no guidance is given as to the possible identity of the relative test or control values.

Applicant points out that a patient rarely has only one disease or disorder, and that their "survey" or recently issued claims regarding diagnosis based on differential gene expression rarely, if ever contain a limitation that the diagnosed patient not be afflicted with an additional disease or disorder. Every case is examined on its own merits. Here, there is evidence on the record that this assay would be invalid or non-functional when co-morbidities are present.

The rejection is maintained.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday or Wednesday, from 9:00 AM until 4:30 PM, and Friday from 12:30 PM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is

(571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

October 9, 2008